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Effects Cytotoxic and Genotoxic of Aqueous Extract of Fennel (*Foeniculum vulgare*var. vulgare Mill.)

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Abstract— *Fennel (Foeniculum vulgare Mill), originating in the basin of the Eastern Mediterranean and Caucasian, is now cultivated in many varieties selected by the sweetness and low concentrations of anethole, which allows consumption in salad dressings and condiments. Other varieties were selected to obtain high concentrations of essential oils and are used in folk medicine pharmaceutical industry. Despite the long history of application ethnomedicinal F. vulgare, no reports of serious side effects, several studies have shown that they can present cytotoxic and genotoxic activity. Therefore, this study aimed to analyze the cytotoxic and genotoxic effects of aqueous extract of fennel (Foeniculum vulgarevar. vulgare Mill.), Prepared in 2%, 4% and 8%, compared to bioindicators (Allium cepa L. and Musmusculus L.). The aqueous extract of F. vulgarea concentration of 2% cytotoxic effects caused significantly inhibiting mitotic division and genotoxic effects, providing chromosomal damage induced micronucleus formation in meristematic cells of Allium cepa L. In experimental animals in vivo genotoxic potential was found in cell bone marrow of mice. In this way, fennel tea should be consumed with moderations and medical care, especially for infants who have not yet developed the digestive tract, it may be harmful to health.*

Keywords— ***Cytotoxicity, genotoxicity, Foeniculum vulgare var. vulgare Mill.***

Key Contribution:*In many homes in Brazil it is possible to find fennel, this in turn, is widely used in traditional Brazilian medicine indiscriminately, it is expected that from this publication encourage new research with this plant, since, it is notorious its toxic effects.*

I. INTRODUCTION

Determined in 2009 by the Ministry of Health of Brazil as a herbal medicine for antiseptic use, from 71 medicinal plants, *Foeniculum vulgare* Mill, popularly known as fennel or fennel, in folk medicine is indicated, especially in relieving problems digestive, to eliminate gases, combat cramps and stimulate lactation (1).Botanical drugs are very complex sources of bioactive substances that can act on different "druggable" targets (2).

Although there are different nutritional values in different organs, upper parts are the most used for therapeutic and culinary purposes. Since pharmacological compounds are veryvolatile, such as anethole, estragole, trans-anethole and camphor, which give flavor and characteristic smell of fennel. In these compounds, the upper parts contain major metabolites such as flavonoids, coumarins, phenolic taninoseácidos(3).

In foliar aqueous ethanolic extracts of fennel is extracted several phenolic compounds, and specifically in aqueous, phenolic acids are identified six (3-o-, 4-O- and 5-O-caffeoylquinic; acid The 1,3- - 1,4-O- and O-1,5-dicaffeoylquinic) three flavonoids (eriodictyol-7-Orutinósido, quercetin-3-Orutinósido and quercetin-3-O-glucuronide) and rosmarinic acid, all considered pharmaceutical interest (4).

Several pharmacobotanic work have demonstrated the medicinal efficiency of fennel, both to treat simple diseases (respiratory and digestive tract), and treat more complex diseases, such as cancers.

The common effects on diseases of the respiratory and digestive tracts can be explained by antispasmodic actions of volatile compounds that stimulate the contraction of smooth muscles of their bodies. Since the effects on tumor cells have been linked

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to the action of caffeic acid 5-O-caffeoylquinic, thatcan display inhibition of cell growth, inducing cell cycle arrest in the G1 phase (3).

Researchersdescribe antifungal and antibacterial activities of aqueous leaf extract of *F. vulgare* on *Candida albicans* and *Staphylococcus aureus*(5).

A long history in etnomédica application without any reports of serious side effects, suggests that *F. vulgare* can be considered safe (6). However, no work described above on the phenotypic plasticity, which *F. vulgare*, can be provided for different concentrations of metabolic compounds according to the environment in which it is planted.

Severalstudies performed with *F. vulgare* from different geographical origins and different varieties indicate that the contents of estragole in fruits can vary from 2% to 86% and the trans-anethole from 0% to 89% (7).According to Simões*et al.* (1999), the environment in which the plant grows exertsgreat influence on production and the compositionofthe chemistry included in the essential oils(8). Temperature, relative humidity, duration of sun exposure and wind regime can have a direct influence, especially on species that have histological structures of oil storage on the leaf surface, such as *F. vulgare*.

According to Gross *et al.* (2009) compounds, phenylpropanoids, estragole and trans-anetholethe main constituents of the upper parts of *F. vulgare*, and their concentrations can vary during plant development, but the greatest quantities of these compounds independent of the time is in the flowers and the fruits(9). Diaz-Marot*et al.* (2006) examined 42 strains of F. vulgare different geographical areas of central Spain and found that the concentration of the major volatile component, trans-anethole, presented phytochemical variability in the locale(10).

Phytochemical phenotypic plasticity and failure to identify varieties is likely to be a major cause of disputes found in the scientific literature regarding the toxic effects of *F. vulgare*.

In acute toxicity tests *F. vulgare*, Ostad*et al.* (2001) determined the median lethal dose (LD50) of 1,326 mg/kg, with the occurrence of prostration, sedation, respiratory discomfort, movement disorder, apathy to external stimulation, weakness, tremors and fasciculations in the dorsal muscles of the guinea pigs during the first 24 hours of treatment(11).

The Unified Health System (SUS), said in its medicinal plant program publications Central medicines (CEME) that *F. vulgare* is toxic in preclinical toxicology studies (Brazil, 2006).

Detection of potentially cytotoxic and genotoxic substances and their likely effects on organisms, it is important in the sense of the impact that they can bring to people, animals, plants and humans.

Considering the wide use of *F. vulgare* in Brazilian folk medicine and in cooking; and little information on their potential citogenotóxics and genotoxic effects, the use of bioassays are needed to provide reliable information to the public.

Thus, this study aimed to assess and verify the cytotoxic effects and genotóxic effects of aqueous leaf extract *Foeniculum vulgare* var. vulgare Mill. on bioindicators.

II. RESULTS AND DISCUSSION

2.1System Test plant

In Table 1, it appears that aqueous leaf extract of fennel to 2%, relative to the CN, significantly inhibited mitotic division ofmeristematic cells of A. cepa, as the analyzed index (IMT, IP, IM, IA, IT) demonstrated in this way possible to prepare substances extracted in the aqueous extract can be actuated by inhibiting the cell cycle. One possible explanation for this result could be the action of various phenolic compounds found mainly in parts of areas *F. vulgare*, such as those derived caffeoylquinic, 3-Ocafeoilquinico acid, 4-and 5-Ocafeoilquinico Ocafeoilquinico(12, 13); and according comKrizman*et al.* (2007), they can be easily extracted from the preparation of the aqueous extract of fennel(4).

Table.1: Mean values of Mitotic indices (IMT) prophases (IP) of metaphase (MI) of anaphases (IA) and the telophases (IT) of negative control (NC), positive control (PC) and treated with aqueous extract of Foeniculum vulgarevar. vulgare Mill. to 2%.

Treatments	IMT	IP	IM	IA	IT
CN	0.549	0.293	0.110	0.071	0.036
2% *	0.025	0.015	0.014	0.002	0.004
CP	0.023	0.017	0,020	0.009	0.007

* (P <0.01)

With respect to IMT, IP, IM, IT IA and the control group (1% glyphosate), it was found that the aqueous extract of fennel 2% showed similar results (p> 0.05) in reference to inhibition of cell cycle.

According Zablotowicz and Reddy (2004), glyphosate mechanism of action is rather unique because it is the only herbicide capable of specifically inhibiting the enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS), which catalyzes the condensation of shikimic acid and pyruvate phosphate, thus preventing synthesis of three essential amino acids - tryptophan, phenylalanine and tyrosine, which are precursors of phenolic compounds(14).

In specific literature allelopathy, there are several studies that show the phenolic compounds act affecting the germination and growth of plant species test, by

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interfering with cell division, enzymatic activation, and membrane permeability (15-19).

The cytotoxic activity of fennelwas verified studies Tanira*et al*. (1996), in which the authors found a significant decrease in significant IMT in animal testing system of mice, indicating a significant antimitotic activity, furthermore, the ethanolic extract of the fruits of the plant at doses of 0.5, 1.0 and 3.0 $g.kg^{-1}$ administered orally, did not cause any deaths in mice(20).

Apart from causing potential cytotoxic effects of the substances extracted in the aqueous extract of fennel 2% promoted damage on the chromosomes, inducing the formation of micronucleous (0.25%) in total analyzed blades, the roots of A. cepa (FIGURE 1). Other chromosomal abnormalities were observed, probably the small number of cells in the mitotic division in this concentration (TABLE 1).

With regard to the percentage changes found, the CP group (1% glyphosate), who has caused the largest percentage of damage to chromosomes (0.87%) significantly different from the other treatments studied, as expected ($p < 0.05$). Similar results were also observed by Souza *et al*. (2010)(21).

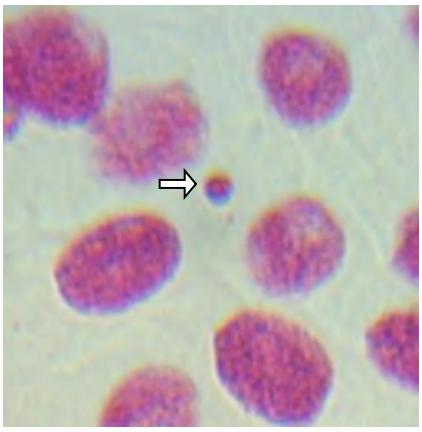

Fig.1: Micronucleus (arrow) in meristem cells of Allium cepa treated with aqueous extract of Foeniculum vulgarevar. vulgare Mill.to 2%. total increase of1000×.

The micronuclei usually result in production or acentric chromosome fragments entire chromosomes in which lag anaphases. When the cell enters telophase, these are included in the daughter cells.

Was one of the first investigators who demonstrated the relevance of tonea system strain for the assessment of cytotoxicity and genotoxicity of organic substances, claiming the cells of roots strain have an important system of enzymes necessary for the activation of mutagens (22).

The same author also demonstrated that the sensitivity of the Allium test is on par with other systems, such as algae or human lymphocytes. In the case of mercury toxicity test, Allium test, demonstrated similar values to the test performed in humans in vivo (22).

Currently several studies have proven the test efficiency A. strain for monitoring the cytotoxic and genotoxic effects of various organic substances (23)Çelik and Aslantürk, 2010; (24-26), as observed in the present study with aqueous extract of *Foeniculum vulgare* in 2%.

2.2Animal Testing System

The results within and between groups were analyzed by ANOVA and Tukey test ($p<0.05$) for comparison of means. After analysis it was found that there was a significant difference in the mean micronuclei (MN's) of the treatments tested for the groups CN and CP. Among the averages MN's concentrations of 4% and 8%, there was no significant difference, but the same were significantly higher than the average of the CN group to 2%; and smaller, as expected, that the CP, showing, in this way, the average number NM increased as the concentration increased the aqueous leaf extract *Foeniculum vulgare* Mill (TABLE 2).

Table.2: Total and mean number of micronuclei (MN's) erythrocytes in mice (Musmusculus L.)induced by treatment of the aqueous leaf extract Foeniculumvulgarevar. vulgare Mill.

	Treatments				
Repetition	CN	2%	4%	8%	CP
I	1	11	34	33	68
II	3	13	19	29	57
III	3	8	27	27	70
IV	2	13	30	39	64
Averages	2.25 *	11.25 *	27,50ns	32,00ns	64.75 *

***** Significant difference at 1% probability by Tukey

ns - there is no significant difference

These results indicate that the aqueous extract of fennel, at the concentrations tested, have potentialclastogenic to promote chromosomal damage or damage to the mitotic apparatus in the formation of erythroblasts in bone marrow of mice.

The NRBC mammalian Extrude its core in the terminal stage of maturation, which are subsequently phagocytized by macrophages. However, when the nuclei of erythroblasts DNA is damaged by clastogenic substances are formed and remain micronuclei in polychromatic erythrocytes and are readily identified after staining(FIGURE 2).

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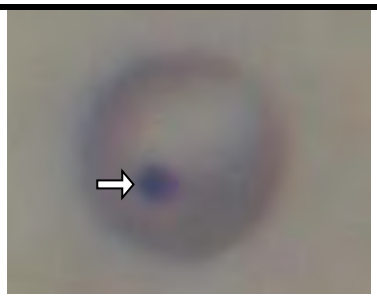

Fig.2: Micronucleous (arrow) in mice erythrocytes (Musmusculus L.) gives Swiss strain exposed to aqueous extract of Foeniculum vulgare var. vulgare Mill.in 8% (500 mg.kg^{-1}) orally single dose. Total increase of 400×.

Regarding the presence of many active biological constituents in *Foeniculum vulgare*, Devika and Mohandass (2014), studied the apoptotic activity of the crude extract methanólic fennel leaves in cell lines of cervical cancer (HeLa)(27). Induction of apoptosis was determined by analysis of DNA fragmentation in cervical cancer cells treated with active fraction of the crude methanol extract using agarose gel electrophoresis. The DNA fragmentation was observed at different concentrations of the extract and morphological features of apoptosis bodies were observed in a concentration of 125µg.ml^{-1} extract. The results suggested *F. vulgare* could probably induce apoptosis in cell lines of cervical cancer and inhibit cell proliferation by DNA fragmentation.

DNA fragmentation was also verified in the present study through the micronucleus test in mice erythrocytes (FIGURE 2 AND TABLE 2).

Tang and Edenharder (1997) showed that the fennel leaves extracts show moderate activity mutagenic in strains of *S. typhimurium*TA98(28).

Sharopov*et al*. (2017) found the cytotoxic effect of essential oil *F. vulgare* various cancer cell lines,HeLa (human cervical cancer), Caco-2 (human colorectal carcinoma), MCF-7 (human breast adenocarcinoma), CCRF-CEM (human T lymphoblast leukemia) and CEM / ADR5000 (adriamycin resistant leukemia). The reseachers show that the essential oil is rich in *F. vulgare* lipophilic secondary metabolites, which can easily cross cell membranes by diffusion and react with free amino groups of amino acid residues of proteins or nucleotides of DNA, forming Schiff bases(29).

Mirfendereskie*et al*. (2012) found the toxic effects of decoctions of fennel seeds traditionally used in Iran as a herbal remedy(30). The genotoxicity and cytotoxicity was assayed in vitro using Allium cepa L. roots and human cells. The decoctions seeds were prepared in the traditional method commonly used in Iran (DC) to 10 times concentration (10C). Although both extracts have decreased IMT cells nose root of A. cepa L., only 10C extract significantly increased chromosomal aberrations. Furthermore, dilutions 1:30, 1: 62.5, 1: 125 and 1: 250 10C 100% extract were cytotoxic to human lymphocyte cells, however, to extract the DC only showed 1:30 dilution cytotoxic effects.

Several studies suggest beneficial effects and adverse *F. vulgare* in relation to this work, such as effects antioxidants and anti-clastogenic(31-34)however, all these studies were performed withessential oil, whose substances are not extracted in aqueous and alcoholic extracts and / or seeds.

One of the great controversy with ethnomedicinal studies are related to species identification difficulties and / or varieties that may present physiological phenotypic plasticity of secondary metabolites in addition to the main problem, which is the study of crude extracts, which do not indicate what substances arereally bioactive and in what concentrations they act.

Pimenov and Leonov, (2004) reported that there are some morphologically similar species to *F. vulgare*, which make it difficult to identify(35). Simoes*et al*. (1999) report the *Foeniculum vulgare* Mill similarity between *Pimpinella anisum* L. and which are commonly known as fennel(8).

Fenneloriginated inthe basin of the Eastern Mediterranean and Caucasian, is now cultivated in many varieties (36)selected by the sweetness and low concentration of anethole, which allows consumption in salads. Other varieties were selected to obtain high concentrations of essential oils and are used for perfumery and for the production of flavorings.

By way of exemplificationwe present some variety: *Foeniculum vulgare* Mill. subsp. vulgare var. azoricum (Mill.) Thell; *Foeniculum vulgare* Mill. subsp. vulgare var. dulce (Mill.) Batt .; *Foeniculum vulgare* Mill. var. azoricum (Miller) Thell .; *Foeniculum vulgare* Mill. var. Juice ALCF .; *Foeniculum vulgare* Mill. var. Duke Alef .; *Foeniculum vulgare* Mill. var. duke Batt. &Hold .; *Foeniculum vulgare* Mill. var. Duke (Mill.) Battand. &Trabut and *Foeniculum vulgare* Mill. var. salivumPresl.

Despite the long history of application etnomedicinal *F. vulgare*, no reports of serious side effects, the present study and other above, one can notconsider it a safe species, particularly for infants who do not have the digestive tract developed. However, the diverse and proven pharmacological activities *Foeniculum vulgare* show there is still a huge scope to chemical exploration.

In many homes in Brazil it is possible to find fennel, this in turn, is widely used in traditional Brazilian medicine indiscriminately, in several places is also consumed as food, it is expected that this document will awaken several researchers to deepen their knowledge regarding this plant.

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III. MATERIAL AND METHODS

3.1Collection of botanical material

Parties flights *Foeniculum vulgare*var. vulgare Mill.(Stems and leaves) were collected at the site of medicinal plants of the Center for Biological Studies - UNEC (19 ° 47 '23 "S, 42 ° 08' 21" W), in May, the morning in shaded conditions. Immediately after collection, the upper parts were packed in sterile plastic bags and brought to the lab pharmacobotanics UNEC to prepare the aqueous extract, thesample specimen is deposited in the UNEC-0305042016 * and was identified by.

3.2 Preparation of the aqueous extract of fennel

The aqueous extract was prepared according to popular Brazilian ethnobotany 20g of fresh leaves in 1L of boiled water, making up the extract at 2%, after reaching room temperature Later, using the same methodology, the extracts a4% and 8%, aiming the determination of the dose response relationship.

3.3 System test plant (Allium cepa L.)

Experimental units composed of 8 repeats of bulbs of similar size and weight,*A. strain* newly rooted were placed for 24 hours in distilled water (negative control - CN), the concentration of the aqueous extract of fennel commonly used by people (2%) and glyphosate in a 1% solution (positive control - CP) .Posteriormente, the roots of approximately 5 mm were collected and fixed in Carnoy and stained in Schiff reagent. 2.000 meristematic cells were analyzed on 5 plates per treatment were determined and the mitotic index (IMT) prophases (IP) of metaphase (MI) of anaphases (IA) and the telophases (IT) per slide. All meristematic cells of all slides per treatment were analyzed to check alteraçõescromossômicas(37).

It took only the concentration of the extract to 2%, this test system, because it did not occur cytotoxic and genotoxic changes, the test animal's system would not be realized, avoiding in this way the use of guinea pigs.

3.4 System Test Animals (*Musmusculus* L.)

mice were used in theSwiss strain, Adults with an average weight of 28g.The animals spent 6 days adjustment period, with water and food ad libitum commercial environment with a photoperiod of 12h light and 12h dark, average temperature of 23 °C mice Groups of 4 rats were treated with aqueous extracts of fennel, orally, in acute treatment, the three experimental concentrations (2%, 4% and 8%). For the negative control (NC) was used distilled water and the positive control (PC) was used cyclophosphamide, 24hours before euthanasia. The genotoxicity was evaluated by counting all erythrocytes micronuclei (MN) in the bone marrow smears from each femur in each treatment, comprising two blades repeats (38).

All solutions (extracts, CN and CP) were administeredby gavage a single dose of 50mg/kg, introducing special needle through the mouth into the stomach of the animal, and the like via the accidental or intentional ingestion of the test substance. This research is duly authorized by the CEP/UNEC.

3.5 Statistical analysis

The experimental design for each evaluation test system was randomized (DIC) using variance analysis method (ANOVA) and subsequent Tukey test for the comparison of averages, at 5% probability.

IV. CONCLUSIONS

- The aqueous extract of *Foeniculum vulgare* var. vulgare Mill.At a concentration of 2% cytotoxic effects caused significantly inhibiting mitotic division and genotoxic effects, providing chromosomal damage induced micronucleus formation in meristematic cells of Allium cepa L.
- *Foeniculum vulgare* var. vulgare Mill., in the vivo experimental model used, it shows genotoxic potential in bone marrow cells of Swiss strain mice.
- The fennel tea should be consumed with moderations and medical care, especially in infants, it may be harmful to health.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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